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REMARKS

Claims 64, 65, 70-72, 76-78, 80-83, 85-87, and 149-163 are pending and under consideration. Claims 64, 80-82, 149, 151, 153, and 161 have been amended herein. Claims 70 and 162 have been canceled, without prejudice. Claim 164 has been added. After entry of the present Amendment, claims 64-65, 71-72, 76-78, 80-83, 85-87, 149-161 and 163-164 will be pending and under consideration.

The amendments submitted herewith are supported by the specification and original claims and do not add new matter. The amendment to claim 64 that the skin is tape stripped between one and twelve times, and newly added claim 164 are supported by the description of Figure 1 (page 4, line 20), and page 19, lines 8-9. The amendment to claims 149 that the adhesive is applied one or more times, is supported by page 3, lines 14-15. The amendments to claims 151, 153, and 161 are grammatical in nature, and as such do not substantively change the claims. Entry of the amendments is respectfully requested, as well as reconsideration of the pending claims in view of the amendments and remarks herein.

Per the Examiner's request, included with this filing as Exhibit D is a copy of the Supplemental Amendment filed July 22, 2002.

Claim Rejection Under 35 U.S.C. §112, Second Paragraph

Claims 65, 149-156, and 161 stand rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite. Applicants respectfully traverse the rejection. As a preliminary note, although the first line of the rejection indicates that the rejection is directed at claim 163, the body of the rejection cites claim 161 not claim 163, and based on a review of these claims, the rejection appears to be directed at claim 161. Therefore, Applicants analyze the rejection as directed against claim 161.

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The Office Action alleges that claims 65 and 161 are indefinite as being duplicative because it is not clear to the Examiner how the sample could comprise cells "associated" with the stratum corneum without also comprising stratum corneum cells themselves. It is well-established in the art that during certain dermatitis conditions cells infiltrate the stratum corneum that are not part of the stratum corneum proper. For example during conditions such as psoriasis and mycosis fungoides, as well as superficial crusting conditions such as impetigo and eczema, inflammatory cells of the circulation, such as neutrophils and lymphocytes, infiltrate the stratum corneum (See e.g., "Dermal Pathology," ed. J H Graham, W C Johnson, and E B Helwig, Harper-Row, Hagerstown, MD, Chapter 6 "Basic pathologic changes in skin" by James H Graham, see pp 119-135, 125-126 (1972) (Exhibit E)). Therefore, a skilled artisan will recognize that the methods of the present invention for isolating or detecting a nucleic acid sample from a skin sample that includes the stratum corneum, when used with certain skin samples, will also isolate cells that are associated with the stratum corneum but that are not part of the stratum corneum proper. Accordingly, Applicants respectfully request withdrawal of the rejection of Claims 65, 149-156, and 161 under 35 U.S.C. §112, second paragraph.

The Office Action alleges that claim 149 and dependent claims 151 and 153 are indefinite in reciting "such that" because it is alleged that no method steps are recited that would specifically result in the desired outcome. Claim 149 as amended herein recites that an adhesive tape is applied and removed from the skin to isolate an RNA, as suggested in the Office Action. Claims 151 and 153 are amended in a similar manner. Applicants graciously acknowledge the Examiner for her suggestion. Accordingly, Applicants respectfully request withdrawal of the rejection of Claims 149, 151 and 153 under 35 U.S.C. §112, second paragraph

Claim Rejection Under 35 U.S.C. §112, First paragraph

Claims 71, 82, 156, 159, and 160 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter that was not described in the specification in such a way as to

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reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicants respectfully traverse the rejection. The specification must be read from the point of view of a skilled artisan. 35 U.S.C. §112, first paragraph. A description is presumed to be adequate, unless or until sufficient evidence or reasoning to the contrary has been presented by the examiner to rebut the presumption. MPEP § 2163.04.

Regarding claims 72 and 156, the Office Action alleges that there is no support in the specification for embodiments in which the skin is stripped 1-2 times. The Office Action acknowledges that there is support in the specification for stripping 1 time, 1 or more times, or 1-25 times. However, the Office Action alleges that there does not appear to be a contemplation of stripping 1 or 2 times, apparently because this range is not explicitly recited in the specification.

Based on the teachings of stripping 1 or more times (Page 3, lines 14-15) and up to 25 times (Page 18, line 4), as well as the experimental use of 12 tape strippings (Figure 1, page 4, line 20, and page 19, lines 8-9), a skilled artisan will recognize that tape stripping one or two times is within the range of the invention contemplated by the inventors and can be successfully employed in the methods of the invention. Applicants respectfully assert that a conclusion that stripping 1-2 times is not supported by a disclosure of 1 or more times and 1-25 times, for example 12 times, improperly concludes that only language that is explicitly and literally present in the specification provides adequate support for claim terms. The MPEP summarizes the law on literal support for claim terms indicating that "the subject matter of the claim need not be described literally (i.e., using the same terms or in *haec verba*)."

MPEP §2163.02. The burden rests with the Patent Office to provide reasons for why the description in a recited embodiment must be supported literally by the specification. (In re Wertheim, 541 F.2d 257, 191 USPQ 90, 98 (CCPA)(1976)). The only rationale given in the pending Office Action for this rejection, is that the claim language does not explicitly state tape stripping one or two times. Therefore, the rejection is improper because it does not provide reasons for why in this situation, the specification must literally support the claim term.

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The present situation is analogous to that of In re Wertheim. In Wertheim, the appellate court held that a range of between 35% and 60% percent solids in a process for freeze-drying coffee was supported by a disclosure that included a range of 25%-60% percent solids and specific examples of 36% and 50%. Id. at 98. The Wertheim court distinguished between the claims at issue in that case, which were directed at processes and their parameters, and chemical cases, in which chemical species may not be supported by disclosure of a broad generic chemical compound. The court held that a process parameter range not literally disclosed, but within a broader literally disclosed range is adequately described if based on the specific parameters used in examples and broader disclosed range, a skilled artisan would recognize that the range was contemplated and could be successfully employed. Id. A skilled artisan will recognize that the present specification's teaching of tape stripping 1 or more times, up to 25 times, and the experimental use of 12 tape strippings, provides sufficient support that 1 or 2 tape strippings was contemplated as within the parameters of the claimed methods, and could be successfully employed in the claimed methods.

The only reason provided by the Patent Office in the prosecution history of the present case that the specification does not support tape stripping 1 or 2 times, besides a lack of literal support, was provided in a previous Office Action in which it was stated that one or two tape strippings is not supported because "there is no evidence of conception of criticality of stripping the skin only one or two times." Office Action mailed December 12, 2002, Page 6, lines 20-21. However, it is not necessary to meet the requirements of 35 U.S.C. §112, first paragraph to identify a critical range. What is required, as indicated above, is that a skilled artisan recognizes that the range was within that contemplated by the inventors as part of their invention, and could be successfully employed in the invention. In re Wertheim, at 98. The Office Action acknowledges that the specification supports tape stripping one time and one to twenty five times. Furthermore, the specification experimentally shows that 12 tape strippings can be successfully employed. Finally, the Office Action in its prior art rejection asserts that minimizing the number of applications of tape required to obtain a sufficient sample size would be obvious to a person of ordinary skill in the art. (Office

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Action page 6, lines 8-11). The Applicants agree with this statement in view of the teachings of the present specification, which, unlike the prior art, indicate that in certain embodiments it is desirable to perform as little as 1 tape stripping. Therefore, a skilled artisan will recognize that one or two tape strippings is within the contemplated range of tape strippings, and can be successfully employed in the methods of the present invention. Accordingly, Applicants respectfully assert that claims 72 and 156 are adequately supported by the disclosure as filed.

The Office Action asserts that claims 159-160 in reciting the phrase "an external agent that causes dermatitis before applying the adhesive tape" is new matter because allegedly the specification does not disclose causing dermatitis as part of the invention, and allegedly does not give any reason to do so. Applicants respectfully assert that the specification provides support for applying an external agent to cause dermatitis. For example, the specification discloses that in one embodiment the invention provides a method for identifying a compound that causes dermatitis by contacting a section of skin with a test compound (page 4, lines 7-11). Furthermore, the specification provides details regarding how such a method can be performed (page 16, line 21 to page 17, line 12).

Support for this phrase is also provided by Example 2. The Office Action alleges that Example 2 merely provides a test system in which contact dermatitis is induced using SLS for the purpose of detecting changes in the cytokine expression. Applicants respectfully assert that Example 2 provides a reduction to practice of the invention of claims 159 and 160 since it illustrates contacting the skin with an external agent before tape stripping and isolating nucleic acids. Reduction to practice is one way to establish possession of an invention to meet the written description requirement of 35 U.S.C. §112, first paragraph. MPEP §2163.02. Thus, Applicants respectfully assert that in addition to the specification sections cited above, Example 2 supports claims 159 and 160. Accordingly, Applicants respectfully assert that claims 159 and 160 are adequately supported by the disclosure as filed.

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With respect to claim 82, the Office Action alleges that the specification does not enable detection of nucleic acids encoding leukotrienes and prostaglandins because allegedly neither substance is encoded by nucleic acids. Applicants traverse the rejection. Claim 82 does not recite detection of nucleic acids encoding leukotrienes or prostaglandins. Rather, claim 82 recites that the nucleic acid isolation includes a nucleic acid that encodes interleukin-1 (IL-1), interleukin-2 (IL-2), interleukin-3 (IL-3), interleukin-4 (IL-4), interleukin-5 (IL-5), interleukin-6 (IL-6), interleukin-8 (IL-8), interleukin-10 (IL-10), interleukin-12 (IL-12), interleukin-13 (IL-13), granulocyte macrophage colony stimulating factor (GM-CSF), or an interferon, or any combination thereof. Accordingly, Applicants respectfully request withdrawal of the rejection of Claims 71, 82, 156, 159, and 160 under 35 U.S.C. §112, first paragraph.

Rejections Over Prior Art

Claim Rejections Under 35 U.S.C. §102 and §103

Claims 64, 65, 70, 76, 85, 86, and 161-162 stand rejected under 35 U.S.C. §102(b) as allegedly being anticipated by or in the alternative under 35 U.S.C. §103(a) as obvious over Garofano et al., *Adv. Forensic Haemogenet.*, 6:281-83 (1996). Applicants respectfully traverse the rejection. To anticipate an invention, each and every element of a claim must be found in a single prior art reference. MPEP §2131; *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). To establish a *prima facie* case of obviousness there must be some suggestion or motivation in the prior art to make the claimed invention, there must be a reasonable expectation of success, and the prior art reference must teach or suggest all of the claim limitations. MPEP §2142; *In re Vaack*, 947 F.2d 488, 20 USPQ2d, 1438 (Fed. Cir. 1991). Furthermore, in order to render a claimed apparatus or method obvious, the prior art must enable the invention. *Beckman Instruments, Inc. v. LKB Produkter AB*, 892 F.2d 1547, 1551 (1989); and *Rockwell Int. Corp. v. United States*, 147 F.3d 1358, 1364, 7 USPQ2D (BNA) 1027 (Fed. Cir. 1998).

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The Office Action alleges that Garofano et al. disclose a method of obtaining a DNA skin sample by applying adhesive tape to the skin.

With respect to the rejection under 35 U.S.C. §102(b), claim 64, from which the remaining rejected claims depend, recites that the adhesive tape is applied between one and twelve times. Garofano et al. disclose tape stripping "until the adhesive power of the tape was lost" (pg. 281, paragraph starting "All samples were obtained..."). Garofano et al. is silent as to how they determined that the adhesive power was lost. Therefore, from the disclosure of Garofano et al., it is not possible for a skilled artisan to determine precisely how many times the adhesive tape was applied to the skin, as acknowledged in the Office Action. However, as set out below, it appears that Garofano et al. used more than 12 tape strippings to obtain samples.

As indicated in the attached Declaration of Dr. Nicholas Benson (Exhibit A), by the teaching of stripping until the adhesive power is lost, Garofano et al. teach a method that utilizes more than 12 tape strippings. In an experiment performed by Dr. Benson using tapes that were similar to those used by Garofano et al., it was determined that at least 15 tape strippings for an individual experiment were required before the adhesive power of the tapes was lost, and on average per subject at least 22 tape strippings were required. Furthermore, when stubs were used, which Garofano et al. concluded were preferred (page 282, penultimate paragraph), in every case more than 25 applications were required for the stubs to lose their adhesive power. Therefore, Applicants respectfully assert that Garofano et al. do not disclose a method for isolating or detecting a nucleic acid sample from a skin sample wherein adhesive tape is applied to the skin and removed between 1 and 12 times. Accordingly, Applicants respectfully request withdrawal of the rejection of Claims 64, 65, 70 76, 85, 86, and 161-162 under 35 U.S.C. §102(b).

With respect to the rejection of claims 64, 65, 70, 76, 85, 86, and 161-162 as obvious under 35 U.S.C. §103(a) over Garofano et al., *Adv. Forensic Haemogenet.*, 6:281-83 (1996), from the disclosure of Garofano et al., Garofano et al. is silent, and a skilled artisan would not expect a

reasonable chance of success, or be motivated to isolate nucleic acids from skin cells using only one to twelve tape strippings. Garofano et al. report a relatively "low percentage of positive results" (page 282, last paragraph) even when tape stripping until the adhesive power was lost, which as discussed above, involves more than 12 tape strippings. Accordingly, one of ordinary skill in the art would not reasonably expect to successfully isolate DNA from skin using only between 1 and 12 tape strippings, and would not be motivated to use 1 to 12 tape strippings. Furthermore, there is no teaching in Garofano et al. of using 1 to 12 tape strippings, or of using less tape strippings than required for the tape to lose its adhesive power.

Additionally, Garofano et al. do not provide a reasonable expectation of success or an enabling disclosure for the isolation of DNA using one to twelve tape strippings, because they fail to include the necessary controls to establish that the DNA isolated from any of the small number of positive samples, in fact originated from the sampled skin, instead of as a processing contaminant. It is well known that amplification reactions are very sensitive to contamination (See attached Declaration of Gerald Krueger (Example B)). Therefore, in studies aimed at demonstrating the success of a sampling technique that utilizes an amplification step, a control is typically included to establish that the amplified DNA originates from the sample, and is not a contaminant. Although Garofano et al. report that blood samples were taken from the individuals in their study, no data is presented which compared nucleic acids of the blood sample to the tape stripping sample to confirm that amplified DNA originated from the tape stripping sample rather than as a contaminant. Accordingly, Applicants respectfully assert that Garofano et al. do not provide a reasonable expectation of success, do not provide motivation, and do not provide an enabling disclosure regarding the method of claim 64, and claims dependent therefrom. Therefore, Applicants respectfully request withdrawal of the rejection of Claims 64, 65, 70, 76, 85, 86, and 161-162 under 35 U.S.C. §103(a).

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Claims 71-72 were rejected under 35 U.S.C. § 103(a) over Garofano et al. *Adv. Forensic Haemogentet.* 6:281-83 (1996). Applicants respectfully traverse the rejection. The Office Action cites the allegations regarding Garofano et al. in the above rejection, and further alleges that with respect to claims that recite one or two tape strippings, it would have been obvious to a person of ordinary skill in the art to determine the minimum number of tape strippings. The Office Action alleges that the skilled artisan would have been motivated to use less tape strippings to minimize stress and trauma on the patient, and alleges that both are well-recognized motivations in the medical arts.

Claims 71-72 recite that adhesive tape is applied to the skin between one and two times (claim 71) or one time (claim 72) to obtain the skin sample. Garofano et al. teach that tape is repeatedly applied "until the adhesive power is lost." The Office Action impliedly acknowledges that this requires more than 2 tape strippings by separating this rejection from the 35 U.S. C. 102 rejection above. As discussed above, at least 15 tape strippings, and on average per subject at least 22 tape strippings are required to exhaust the adhesive power of tapes similar to those used by Garofano et al. (See Declaration of Dr. Nicholas Benson (Exhibit A) and experiments (Exhibit B)). Despite the fact that they tape stripped until the adhesive power was lost (i.e. at least 15 times), Garofano et al. report a relatively "low percentage of positive results" (page 282, last paragraph). Furthermore, Garofano et al. report that it is desirable to use tapes with more adhesive power (Page 282, penultimate paragraph). As recognized by one of ordinary skill in the art and illustrated in the experiment #1 of Exhibit B, tapes with more adhesive power require more tape strippings to lose their adhesive power. Therefore, Garofano et al., teach away from using one or two tape strippings. Accordingly, Applicants respectfully request the withdrawal of the rejection of Claims 71-82 under 35 U.S.C. §103(a) over Garofano et al.

Claims 80-82, which are directed at the isolation or detection of a cytokine (claim 80), an interleukin (claim 81), or specific recited interleukins (claim 82), stand rejected under

35 U.S.C. §103(a) as being unpatentable over Garofano et al. Applicants respectfully traverse the rejection. The Office Action asserts that based on the teachings of Garofano et al. that there were nucleated cells in the sample, and the ability of Garofano et al. to amplify a desired nucleic acid using PCR, it would have been obvious that Garofano's method could be used for the detection of any desired DNA, including those recited in claims 80-82.

As amended, claims 80-82 depend from claim 149, which recites a method for determining an expression profile in a skin sample that includes isolating a skin sample that includes ribonucleic acid (RNA), and isolating or detecting RNA. Garofano et al. report that DNA can sometimes be isolated from skin samples using tape stripping. However, Garofano et al. does not teach, or even mention, the isolation of RNA from skin samples using their tape stripping method.

It is well known in the art that it is much more difficult to isolate RNA samples than DNA samples. This difference is due in large part to the presence of ribonucleases (i.e., RNAases) in samples. As indicated in the present specification, it was well known in the art as of the filing date of the present invention that the skin is a rich source of RNAases. (Page 18, lines 24-26). Furthermore, it is well known that RNA is more difficult to isolate than DNA, especially for very small samples, because isolation of RNA typically includes additional steps (i.e., a reverse transcriptase step to produce cDNA, and a purification step before and after the reverse transcriptase step), each of which involves additional sample loss. Garofano et al. in apparently isolating DNA, report that they achieved a "low percentage of positive results" and suggest that this was the result of the extremely small amount of nucleic acids in the sample (See Garafano et al., pg. 282, last 2 paragraphs). Therefore, based on Garofano's apparent teaching of occasional isolation of very small quantities of DNA using tape stripping, one of ordinary skill in the art would not expect a reasonable expectation of success for isolating RNA. Furthermore, this conclusion is further established by the lack of any published reports, of which the Applicants are aware, of using tape stripping of the skin to isolate RNA, other than the work of the inventors or their assignees (see further details below). Accordingly,

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Applicants respectfully request the withdrawal of the rejection of Claims 80-82 under 35 U.S.C. §103(a) over Garofano et al.

Claims 77-78, 80-83, 149-154, 156-158, and 163 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Garofano et al., in view of Paludan et al., *J. Invest. Derm.* 99:830-835 (1992). Applicants respectfully traverse the rejection. To establish a *prima facie* case of obviousness there must be some suggestion or motivation in the prior art to make the claimed invention, there must be a reasonable expectation of success, and the prior art reference must teach or suggest all of the claim limitations. MPEP § 2142; *In re Vaeck*, 947 F.2d 488, 20 USPQ2d, 1438 (Fed. Cir. 1991). The reference teachings must be sufficient for one of ordinary skill in the relevant art having the reference before him to make the proposed substitution, combination, or other modification. *In re Linter*, 458 F.2d 1013, 1016, 173 USPQ 560, 562 (CCPA 1972). MPEP §2143.01.

The Office Action cites Garofano et al. for teaching using tape stripping to detect DNA in skin samples, but acknowledges that Garofano et al. do not teach detection of RNA. However, the Office Action alleges that the teaching of Paludan et al. that IL-8 mRNA can be assayed in samples obtained by skin scraping, makes it obvious to use the tape stripping method of Garofano et al. to detect mRNA of cytokines. The Office Action asserts that a skilled artisan would have expected success because Garofano et al. disclose that nucleated cells were obtained, which allegedly would be expected to contain RNA, as detected by Paludan et al.

Applicants respectfully disagree with the assertion that it would be obvious to combine Garofano et al. with Paludan et al. to arrive at the invention of the pending claims. Garofano et al. report that DNA can sometimes be isolated from skin samples by tape stripping until the adhesive power of the tape is lost. However, Garofano et al. report that they achieved a "low percentage of positive results" and suggest that this was the result of the extremely small amount of nucleic acids in the sample (See Garafano et al., pg. 282, last 2 paragraphs). Garofano et al. are silent as to using their

method to isolate RNA. This is especially significant because of the known difficulties in isolating RNA as compared to DNA, and the known presence of RNAases in the skin and the additional steps required as discussed above.

Paludan et al. disclose obtaining skin samples by scraping the epidermis with a scalpel. However, Paludan et al. report that "the RNA yield was too small for measurement," and appeared to be below 50 pg, even though they sampled the skin by scraping it until the scraped area was moist. (Paludan et al., pg. 831, last paragraph, right column, pg., 832 third full paragraph, left column, and figure 4). Since they scraped until the scraped area was moist, it is likely that Paludan et al. obtained a sample that included cells below the stratum corneum, and thus a larger skin sample than the tape stripping method employed by Garafano et al. (See Declaration of Dr. Gerald Krueger (Exhibit C)). Furthermore, the fact that Paludan et al. obtained very small quantities of RNA despite scraping until the scraped area was moist, teaches away from using a tape stripping method, which would be expected to provide less sample tissue than a scraping methods. Therefore, one of ordinary skill in the art would not be motivated to use Garofano's tape stripping method, which would be expected to yield lower quantities of RNA than Paludan's scraping method, to obtain an RNA sample from the skin. Furthermore, one of ordinary skill in the art would not expect success in isolating RNA from skin samples using a tape stripping method that was only sometimes successful in providing enough DNA for isolation, especially when taking into account the known difficulties in isolating sufficient quantities of RNA as compared to DNA from a sample.

This lack of motivation and expected success of using Garofano's tape stripping method to isolate RNA from the skin is further established by the fact that Paludan et al. used scraping instead of tape stripping. At the time Paludan et al. was published, skin tape stripping methods were available, and used in examining the localization and distribution of substances applied to the surface of the skin within the *stratum corneum*, and for studying the skin's permeability function. (Rougier et al., *J. Pharm. Sci.*, 76:451-454, 452, left column, second paragraph (1987) (Exhibit F); Holleran et

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al., *J. Lipid Res.*, 32:1151-58, 1155, right column, first paragraph (1991) (Exhibit G); and Rougier et al., *J. Invest. Derm.*, 275-78, 275, right column, fourth full paragraph (1983) (Exhibit H)).

The lack of motivation and expected success of using tape stripping to isolate RNA from the skin is further established by the lack of any published reports of which the Applicants are aware, of such a method, other than the work of the inventors or their assignees. This is especially significant considering that over six years have passed since the publication of Garofano et al. and over ten years have passed since the publication of Paludan et al. This lack of published literature using Garofano's tape stripping method to isolate RNA, is consistent with the observation of Dr. Gerald Krueger, one of at least ordinary skill in the art, that despite his knowledge of sampling methods, including tape stripping methods, the teaching of the pending specification, that tape stripping could be used to isolate RNA, was surprising (See Declaration of Dr. Krueger in Exhibit C). Objective evidence or secondary considerations such as unexpected results, failure of others, and skepticism of experts are relevant to the issue of obviousness and must be considered in every case in which they are present. MPEP §2141; *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 218 USPQ 871 (Fed. Cir. 1983); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 231 USPQ 81 (Fed. Cir. 1986), cert. denied, 480 U.S. 947 (1987). Accordingly, Applicants respectfully request the withdrawal of the rejection of Claims 77-78, 80-83, 149-154, 156-158, and 163 under 35 U.S.C. §103(a).

Claim 155 stands rejected under 35 U.S.C. §103(a) as being unpatentable over Garofano et al. in view of Paludan et al. and further in view of Ramsay et al. (U.S. Pat. No. 6,056,859; Referred to herein as the '859 Patent) and Furcht et al. (U.S. Pat. No. 6,054,277, referred to herein as the '277 Patent). The Office Action cites its reasons for rejection summarized above for Garofano et al. and Paludan et al., and alleges that it would have been obvious to combine these teachings with those of Ramsay et al. and Furcht et al., which both allegedly teach the use of DNA arrays for nucleic acid sequence analysis.

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As indicated above, Garofano et al. and Paludan et al. either alone or in combination do not motivate one of ordinary skill in the art to use a tape stripping method to isolate RNA, or provide one of ordinary skill in the art an expectation of success in using a tape stripping method to isolate RNA. Garofano et al. report a high failure rate despite the fact that they were isolating DNA, which is more easily isolated than RNA. Furthermore, Garofano et al. even when successful, isolated very small quantities of DNA. The method of Paludan et al., which would be expected to isolate a larger sample using a scraping method (as discussed above), reported that very small quantities of RNA were isolated. Therefore, as further supported by the lack of published art other than the inventors and licensees own work, and by the fact that Paludan et al. did not utilize a tape stripping method despite the fact that such methods were known for identifying distribution of a substance in the *stratum corneum* after it is applied to the skin surface, Applicants respectfully assert that it would not have been obvious to combine the teachings of Garofano et al. with those of Paludan et al. to obtain a method that uses tape stripping of skin to isolate RNA.

The '859 Patent relates to a method for staining immobilized nucleic acids, and is silent as to a method for isolating ribonucleic acid from the skin. The '277 patent relates to a microchip and is also silent as to a method for isolating ribonucleic acid from the skin. Accordingly, the '859 Patent and the '277 Patent either alone or in combination with the other cited art, do not provide a motivation to utilize the tape stripping method of Garofano et al. to isolate RNA and do not provide a reasonable expectation of success in combining Garofano et al. with Paludan et al. Accordingly, Applicants respectfully request the withdrawal of the rejection of Claims 77-78, 80-83, 149-154, 156-158, and 163 under 35 U.S.C. §103(a).

Claim 87 stands rejected under 35 U.S.C. §103(a) as being unpatentable over Garofano et al. in view of Paludan et al. and further in view of Frayne et al. (U.S. Pat. No. 5,811,239; Referred to herein as the '239 patent). The Office Action cites its reasons for rejection set out above for Garofano et al. and Paludan et al., and alleges that it would have been obvious to combine these

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teachings with the teachings of Frayne et al., which allegedly teaches detection of DNA sequence variation by PCR, hybridization, and RNAase protection.

As indicated above, Garofano et al. and Paludan et al. either alone or in combination do not motivate one of ordinary skill in the art to use a tape stripping method to isolate RNA, or provide one of ordinary skill in the art an expectation of success in using a tape stripping method to isolate RNA. Garofano et al. report a high failure rate despite the fact that they were isolating DNA, which is more easily isolated than RNA. Furthermore, Garofano et al. even when successful, isolated very small quantities of DNA. The method of Paludan et al., which would be expected to isolate a larger sample using a scraping method (as discussed above), reported that very small quantities of RNA were isolated. Therefore, as further supported by the lack of published art other than the inventors and licensees own work, and by the fact that Paludan et al. did not utilize a tape stripping method despite the fact that such methods were known for identifying distribution of a substance in the stratum corneum after it is applied to the skin surface, Applicants respectfully assert that it would not have been obvious to combine the teachings of Garofano et al. with those of Paludan et al. to obtain a method that uses tape stripping to isolate RNA from skin.

The '239 Patent relates to methods for the detection of single base-pair DNA sequence variation in DNA samples. The '239 Patent is silent as to a method for isolating a ribonucleic acid from the skin. Accordingly, the '239 Patent either alone or in combination with the other cited art, do not provide a motivation or a reasonable expectation of success for a method of determining an expression profile by isolating RNA by tape stripping skin. Accordingly, Applicants respectfully request the withdrawal of the rejection of Claims 77-78, 80-83, 149-154, 156-158, and 163 under 35 U.S.C. §103(a).

In the event any matters remain to be resolved in view of this communication, Examiner is requested to telephone Lisa A. Haile, J.D., Ph.D. at (858) 677-1456 so that a prompt disposition of

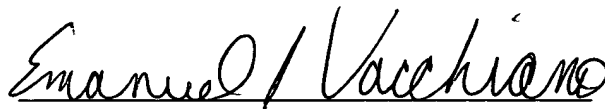
In re Application of:
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this application can be achieved. Please apply any charges not covered, or any credits, to Deposit Account 50-1355.

Respectfully submitted,

Date: September 9, 2003



Emanuel J. Vacchiano, J.D., Ph.D.

Reg. No. 43,964

Telephone: (858) 638-6754

Facsimile: (858) 677-1465

GRAY CARY WARE & FREIDENRICH LLP
4365 Executive Drive, Suite 1100
San Diego, California 92121-2133
USPTO CUSTOMER NUMBER 28213

Enclosures: Exhibits A-I